at page 6, lines 14-26. Support for the amendment of Claim 41 can be found throughout the specification, for example, at pages 15 to 27. Support for new Claims 54-59 can be found throughout the specification, for example, at pages 15 to 27 and FIG. 2. No new matter is added by the amendments.

Summary of the Final Office Action Mailed December 12, 2001

Claims 21and 23-34 stand rejected under 35 U.S.C. § 112 first and second paragraphs and under 35 U.S.C. § 103(a). In addition, Claim 34 is objected to under 37 C.F.R. 1.75(c). Claims 21, 23-34, and 40-53 are also subject to restriction requirement. In addition, the Examiner objects to the drawings, Oath/Declaration and listing of references in the specification. These rejections and objections are addressed below.

Restriction Requirement

In response to Amendment and Response to Restriction Requirement filed on September 27, 2001 (Paper No. 12), the Examiner has issued a Restriction Requirement setting forth the following three groups: Group I (Claims 21 and 23-34); Group II (Claims 40-45); or Group III (Claims 41-53). Claims 40-53 have been withdrawn from consideration by the Examiner as being directed to a non-elected invention.

This Restriction Requirement is being traversed for the reasons set forth below.

The Examiner states that restriction is proper because (1) the inventions of Groups I, II and III are distinct as shown by the different modes of operation, different functions or different effects; and (2) the searches for the different groups are not co-extensive. The Examiner alleges that:

> Group I involves the detection of brain endothelial cell membrane protein and one other marker, Group II involves the detection of any two of the recited markers, while Group III involves the detection of all four markers. Although the methods are directed to the detection of brain injury, they utilized variations from the same group of markers (i.e., myelin basic protein (MBP), beta isoform of S100 protein (S100), neuronal specific enolase (NSE), or brain endothelial cell membrane protein). Therein, the method to assess patient condition, analyzing different numbers of the patently distinct ischemic markers independently or in any combination thereof is directed to diverse and independent markers of the recited method that require different procedural steps and different reagents.

Applicant respectfully traverses.

Applicant first points out that the claims of Group II (Claims 40-45) include claims that require analyzing a body fluid for the presence and concentration of four markers (claims 41-45), as well as claims that require analyzing a body fluid for the presence and concentration of two or more marker proteins (Claims 40 and 42-45).

The inventions of Groups I, II and III are interrelated. Firstly, the methods relate to diagnosing an ischemic or hemorrhagic cerebral event (e.g., brain injury) by analyzing a body fluid of a patient to detect presence and concentration level of marker proteins associated with an ischemic or hemorrhagic cerebral event; comparing the concentration level of the markers proteins to specific threshold values to determine the presence of statistically significant concentrations of the markers; and assessing patient condition in light of the detected markers. The markers to be detected in Groups I, II and III are selected from the same marker proteins, i.e., myelin basic protein (MBP), beta isoform of S100 protein (S100), neuronal specific enolase (NSE), and brain endothelial cell membrane protein). Thus, the inventions of Groups I, II, and III employ the same methods. In addition, the invention of Group I includes embodiments which are also embraced by the invention(s) of Groups II and III. In particular, determining the presence and concentration level of four marker proteins (Group III) embraces determining the presence of one or more marker proteins (Group I) or two or more marker proteins (Group II). As such, the restriction requirement between Groups I, II and III is improper.

Secondly, the Group I claims, the Group II claims and the Group III claims are related to each other as a genus and species. M.P.E.P. §§ 806.04 and 809.02. The claims of Group I entail determining the presence and concentration of one or more marker proteins associated with an ischemic or hemorrhagic cerebral event. The claims of Group II entail determining the presence and concentration of two or more marker proteins associated with an ischemic or hemorrhagic cerebral event. The claims of Group III entail determining the presence and concentration of four marker proteins associated with an ischemic or hemorrhagic cerebral event . Accordingly, Group I is generic to and embraces Group II and Group III. The methods defined in the three groups overlap in the mode of operation and function. As such, the restriction requirement set forth is improper.

In addition, Applicant submits that the examination of Groups I, II and III together would not place an undue burden upon the Examiner. A search of the prior art for the invention of one

group would also identify prior art that is applicable to the other two groups. Furthermore, in light of the close relationship of these inventions, a complete search of one invention would necessarily entail a search of the remaining inventions. For example, a search of prior art for the methods defined by Group I would necessarily identify prior art that is applicable to Groups II and III. As such, Applicant submits that no excessive searching burden would be placed upon the Patent Office in examining Groups I, II and III together.

For the foregoing reasons, withdrawal of the restriction requirement is respectfully requested.

Objection to the Drawings

The Examiner indicates in the Office Action that the Formal Drawings filed on March 30, 2001 have been objected to by the Draftsperson under 37 C.F.R. 1.84 or 1.152. However, it appears from Form PTO 948 attached to the Office Action that the Draftsperson reviewed the drawings filed on July 21, 2000 and apparently did not review the Formal Drawings filed on March 30, 2001. Consideration of the Formal Drawings filed on March 30, 2001 by the Draftsperson is respectfully requested.

Information Disclosure Statement

The Examiner continues to point out that the listing of references in the specification is not a proper Information disclosure Statement. This is not understood.

An Information Disclosure Statement (IDS) was filed on March 30, 2001 (Paper No. 5). The Examiner indicates in the Office Action that this IDS has been considered as to the merits. Clarification of the objection is requested.

Oath/Declaration

The Examiner continues to object to the Oath/Declaration.

A Supplemental Declaration has been forwarded to the inventor, who is presently out of the country, for execution. The executed Supplemental Declaration will be filed at the Patent Office as soon as it is received by Applicant's Attorney.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 21 and 23-34 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Certain claims have been amended in response to this rejection. As amended, the claims even more particularly point out and distinctly claim the subject matter which Applicant regards as the invention. A discussion of each of the specific rejections made by the Examiner follows:

A. Claim 23 has been rejected as vague and indefinite in utilizing the phrase "blood components" because, in the Examiner's assessment, the metes and bounds of the phrase can not be determined as the phrase is not defined in the specification.

Claim 23 has been amended to delete reference to "blood components" and to recite "a blood product." Support for the claim amendment is found in the specification, for example, at page 6, line 7-12, and in original Claim 2. The phrase "blood product" is defined at page 6 to mean a product of blood that contains the markers to be detected. It is believed that this amendment obviates this aspect of the rejection under 35 U.S.C. § 112, second paragraph.

B. Claim 28 has been rejected as vague and indefinite in the use of the term "a single sample" because, in the Examiner's assessment, it is unclear as to whether the phrase is "directed to separate aliquots from the sample wherein the reaction for each marker is separately analyzed" or "a single reaction wherein all the markers are added to a single sample." Applicant respectfully disagrees with the Examiner's assessment that the term "a single sample" renders the claims vague and indefinite.

The test for definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification. Orthokinetics, Inc. v. Safety Travel Chairs, Inc., 1 U.S. P.Q. 2d 1081, 1088 (Fed. Cir. 1986). If the claims read in light of the specification reasonably appraise those skilled in the art of the scope of the invention, § 112 demands no more. Hybritech, Inc. v. Monoclonal Antibodies, Inc., 231 U.S.P.Q. 81 (Fed. Cir. 1987), *cert. denied*, 480 U.S. 0947 (1987).

The specification teaches that a single sample aliquot is used when one assay device is used to measure all the markers and separate aliquots from the same sample are used to measure each marker (page 12, lines 3-16). Thus, one skilled in the art would readily understand the term

"a single sample," when read in light of the specification. As such, the term "a single sample" is definite and the metes and bounds are clear, when read in light of the specification.

C. Claims 21 and 24 have been rejected for their recitation of the phrase "combinations thereof." The Examiner alleges that it is unclear "what combinations are being claimed" and what the phrase is meant to entail.

In an effort to advance prosecution in the subject application, Claims 21 and 24 have been amended to delete recitation of the phrase "combinations thereof." This amendment is not intended to narrow the scope of the claims. It is believed that this rejection is moot in view of the amendment to the claims.

D. Claims 26 and 27 have been rejected as vague and indefinite because, in the Examiner's assessment, it is not clear as to what "cell type specific with respect to" refers to in the claims.

Claim 26 has been amended to recite that the secondary marker protein is from the same cell type as the ischemic marker protein detected. This amendment is not intended to narrow the scope of the claims. It is believed that this amendment obviates this rejection.

E. Claim 34 has been rejected as vague and indefinite because, in the Examiner's assessment, it appears that NSE, MBP, and S100 are detected, but Claim 34 depends from Claim 21, which requires that only one of these proteins be detected. Applicant respectfully disagrees with this assessment.

Claim 21 requires analyzing body fluid to detect the presence of one or more ischemic marker proteins and analyzing body fluid to detect the presence of a brain endothelial cell membrane protein. Claim 34 entails assessing patient condition by concluding from the results of the analyses of Claim 21 the type of brain injury that has occurred.

Notwithstanding the above, in an effort to advance prosecution in the subject application, Claim 34 has been amended to more clearly indicate that the assessment of patient condition is made based on the results of the analyses of Claim 21. This amendment is not intended to narrow the scope of the claims.

F. Claims 21 and 23-34 have been rejected as incomplete "for omitting essential steps, such omission amounting to a gap between steps." In particular, the Examiner states that there are no

claimed steps for washing or removing unbound materials from the reaction solutions during detection of the marker proteins, and no steps that identify reagent and sample contact, thereby forming a detectable complex for diagnosing and/or distinguishing ischemic or hemorrhagic events.

In an effort to advance prosecution in the subject application, Claim 21 has been amended to recite that the diagnosis method includes contacting the marker proteins with a reagent capable of detecting the marker proteins, and removing reagent that does not detect the marker proteins. As Claims 23-34 depend from Claim 21, they also include the noted amendments. Support for this amendment is found in the specification, for example, at pages 13 to 15. This amendment is not intended to narrow the scope of the claims.

Objection to Claim 34 Under 37 C.F.R. 1.75(c)

Claim 34 is objected to under 37 C.F.R. 1.75(c) as being of improper dependent form for failing to further limit the subject matter of a previous claim. The Examiner contends that "Claims 34 necessitates the analysis of all four markers via steps 1-6" but "claim 21 merely requires detection of brain endothelial cell membrane and one other marker." Applicant respectfully disagrees with this assessment for the reasons discussed above in the response to the rejection of Claim 34 under 35 U.S.C. § 112, second paragraph. Withdrawal of the objection is respectfully requested.

Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 21 and 23-34 stand rejected under 35 U.S.C. § 112, first paragraph, as based on a disclosure which is not enabling. In particular, the Examiner alleges that the method of Claim 21 has insufficient steps that are crucial or essential to the practice of the invention. Specifically, the Examiners states that the recited claims do not include the required steps for contact, formation, separation, detection, and correlation directed to the analysis of interest.

As discussed above, in an effort to advance prosecution of the subject application, Claim 21 has been amended such that the method for the differential diagnosis of ischemic and hemorrhagic cerebral events includes contacting the marker proteins with a reagent capable of detecting the marker proteins, and removing reagent that does not detect the marker proteins. This amendment is not intended to narrow the scope of the claims. In view of the amendment of Claim 21, it is believed that this rejection is moot.

Rejection Under 35 U.S.C. 103(a)

Claims 21 and 23-34 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Jackowski (U.S. Patent No. 5,604,105; hereafter "the '105 patent") or Jackowski (U.S. Patent No. 5,710,008; hereafter "the '008 patent") in view of Strand et al. (Stroke 15: 138-144, 1984; hereafter "Strand"), Fassbender et al. (J. Neurol. Sci. 148: 101-105, 1997; hereafter "Fassbender"), Huguet (Lyon Pharmaceutique 44: 187-192, 1993, Abstract; hereafter "Huguet") Sulter et al. (Neurosci. Letters 253: 71-73, 1988; hereafter "Sulter"), or Yatsu et al. (Stroke 26: 177, 1995; hereafter "Yatsu"). In particular, the Examiner states that the '008 patent and the '105 patent differ from the instant invention in not teaching the use of the specific stroke markers MBP, S100, NSE, and a brain endothelial cell membrane protein. The Examiner then states that these markers were well known in the art and were shown to correlate with stroke events. The Examiner concludes that it would have been obvious at the time of Applicant's invention to use known markers for stroke in the method of the '008 patent or the '105 patent, stating that both the '008 patent and the '105 patent teach that many ischemic markers to which antibodies have been produced are well known in the art. Applicant respectfully disagrees with the Examiner's conclusion that the claimed invention was obvious. This rejection is addressed as follows.

As stated in the M.P.E.P. at § 2143, three basic criteria must be met in order to establish a *prima facie* case of obviousness: (1) there must be some suggestion or motivation in the cited reference itself or in the knowledge generally available to one of ordinary skill in the art, to modify the reference; (2) there must be a reasonable expectation of success; and (3) the prior art reference must teach or suggest all the claim limitations. These criteria, as they relate to the rejection of Claims 21 and 23-34, are addressed as follows.

The '105 patent discloses diagnostic tests for assessing chest pain, and the differential diagnosis of chest pain using a combination of markers. For example, the '105 patent discloses methods for differentiating between unstable angina, myocardial infarction, congestive heart failure and other ischemic events affecting the heart. As stated in column 1, lines 52-59, the term "ischemic event" refers to unstable angina and to myocardial infarction. Applicant notes that as used in the '105 patent, the term "ischemic event" does not include an ischemic cerebral event, as recited in the claims of the present invention. In addition, as described at column 14 to column 19, the markers that are assessed in the '105 patent are cardiac molecules, and are typically proteins that pass from the heart cells as the cell become damaged. The '105 patent does not teach or suggest a method for the differential diagnosis of ischemic and hemorrhagic cerebral

events as recited in any of Claims 21 or 23-34. Nor does the '105 patent provide any reasonable expectation of success for a method for the differential diagnosis of ischemic and hemorrhagic cerebral events.

The '008 patent discloses methods for the differential diagnosis of the origin of chest pain, and for differential diagnosis of the origin of chest pain (e.g., differentiating between unstable angina, myocardial infarction, congestive heart failure, and other ischemic events affecting the heart) using a combination of markers. As described in column 13, lines 20-30 of the '008 patent, the term "ischemic event" refers to both unstable angina and to myocardial infarction, but the term does not include cerebral ischemic events. The '008 patent does not teach or suggest that the method for the differential diagnosis of chest pain can be used for the differential diagnosis of ischemic and hemorrhagic cerebral events, and the '008 patent does not provide any reasonable expectation of success of such a method.

The references of Strand, Fassbender, Huguet, Sulter and Yatsu, considered individually or in combination do not remedy the deficiencies of the '105 and '008 patents. Each of these references discloses a single marker protein that can be used in a diagnostic manner. For example, Strand discloses that brain specific myelin basic protein (MBP) in cerebrospinal fluid is a useful marker of cerebral damage in acute cerebrovascular disease. Strand, however, does not teach or suggest any differential diagnosis methods, and certainly does not teach or suggest that MBP can be used in combination with other markers for the differential diagnosis of ischemic and hemorrhagic cerebral events as recited in Claims 21 and 23-34 of the present invention.

Fassbender discloses that S100 protein may represent a useful serum marker of brain damage in acute stroke. In the study described by Fassbender, blood from ischemic stroke patients was assessed for S100 protein concentrations. Patients with hemorrhagic ischemic events were specifically excluded from the study, as noted at page 102 of Fassbender. Since patients with hemorrhagic cerebral events were excluded from the study, Fassbender teaches away from a method for the differential diagnosis of cerebral and hemorrhagic events as recited in Claims 21 and 23-34.

The abstract of Huguet discloses that neuronal specific enolase (NSE) is useful in the evaluation of prognosis and treatment follow up of neuroblastomas and small cell lung carcinomas. Huguet also states that the quantitation of NSE in the cerebrospinal fluid of patients with stroke or transient ischemic attack might be of interest to evaluate the importance of neuronal damage. Huguet, however, does not teach or suggest any differential diagnosis

methods, and certainly does not teach a method for a differential diagnosis of ischemic and hemorrhagic cerebral events using NSE, as recited in Claims 21 and 23-34. Furthermore, Huguet provides no reasonable expectation of success for the method recited in the claims.

Sulter discloses that hyperglycemia during acute cortical ischemic stroke is associated with enhanced neuronal cell death. The conclusion was drawn based on studies in which neuron specific enolase concentrations in patients with cerebral hemispheric stroke were detected. In this study, patients with hemorrhagic ischemic events were specifically excluded from the study, as noted at page 71. Since patients with hemorrhagic cerebral events were excluded from the study, Sulter teaches away from a method for the differential diagnosis of cerebral and hemorrhagic events as recited in Claims 21 and 23-34.

Yatsu discloses the detection of a 67 kilodalton protein in conditioned media of brain endothelial cells, while evaluating the role of nerve growth factor on brain endothelial cells. Yatsu suggests that this novel protein may play a role in strokes by increasing proliferation of cerebral smooth muscle cells. Yatsu provides no further characterization of the 67 kilodalton protein, and therefore it is not known whether the protein is a brain endothelial cell membrane protein, as recited in Claims 21 and 23-34. Regardless of the characterization of the 67 kilodalton protein, Yatsu provides no teaching or suggestion of what type of stroke this protein might be involved, and certainly does not suggest a method for the differential diagnosis of ischemic and hemorrhagic cerebral events as recited in the claims.

The Examiner alleges that:

> it would have been obvious . . . to use known markers for stroke . . . in either method of Jackowski (5,604,105) or Jackowski (5,710,008) because both methods of Jackowski teach that "many ischemic markers to which antibodies have been produce are well known in the art. . . One having ordinary skill in the art would have been motivated to do this because Jackowski (5,604,105) and Jackowski (5,710.008) taught that their method was rapid, accurate, sensitive, and could distinguish an ischemic event.

Paper No. 14, at page 12, last two paragraphs.

Applicant respectfully submits that this rejection is improper because the basis in the cited Jackowski patents relied upon by the Examiner for the desirability of the proposed combination of references is not supported by the cited patents. In particular, as discussed above, the cited Jackowski patents clearly teach that the "ischemic events" therein refer to unstable angina and myocardial infarction and do not include cerebral ischemic events.

Combining the elements of separate references which do not themselves suggest the combination necessary to obtain a claimed invention is generally improper. ACS Hospital Systems, Inc. v. Montefiore Hospital, 221 U.S.P.Q. 929, 933 (Fed. Cir. 1984). The only document of record which suggests the desirability of the proposed combination is Applicant's specification. However, the use of the present specification as an instruction manual or template to piece together the teachings of the prior art is impermissible hindsight. A *prima facie* case of obviousness is established only if the teachings of the cited art would have suggested the claimed invention to one of ordinary skill in the art with a reasonable expectation of successfully achieving the claimed results. In re Vaeck, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Both the suggestion and the reasonable expectation of success must be found in the prior art, not Applicant's disclosure. Id.

The Court of Appeals for the Federal Circuit has stated that "[t]he proper approach to the obviousness issue must start with the claimed invention *as a whole*." See, e.g., Kimberley-Clark Corp. v. Johnson & Johnson Co., 223 U.S.P.Q. 603, 609 (Fed. Cir. 1984). See also Lindemann Maschinenfabrik G.m.b.H. v. American Hoist & Derrick Co., 221 U.S.P.Q. 481, 488 (Fed. Cir. 1984). It is not proper to pick and choose among individual elements of assorted prior art references to recreate the claimed invention. Smithkline Diagnostics Inc. v. Helena Laboratories Corp., 8 U.S.P.Q.2d 1468, 1475 (Fed. Cir. 1988); Akzo N.V. v. International Trade Comm., 11 U.S.P.Q.2d 1241, 1246 (Fed. Cir. 1986).

None of the cited references, alone or in combination, would have suggested the claimed invention to one of ordinary skill in the art at the time the invention was made with a reasonable expectation of success. More specifically, none of the cited references, alone or in combination, teach or suggest a method for the differential diagnosis of ischemic and cerebral events comprising analyzing a body fluid of a patient to detect presence and concentration level of one or more ischemic marker proteins selected from the group consisting of MBP, S100, and NSE, and analyzing a body fluid of the patient to detect presence and concentration level of a brain endothelial cell membrane protein with a reasonable expectation of success. None of the references, alone or in combination, teaches that by detecting the presence and levels of a combination of MBP, S100, NSE, and a brain endothelial cell membrane protein, that a differential diagnosis of ischemic and hemorrhagic cerebral events can be achieved. Moreover, none of the references, alone or in combination, teaches an assessment via the use of an analytical flow chart as instantly claimed. The cited references merely indicate that isolated

elements and/or features recited in the claims are known. This is insufficient to render the claimed invention *prima facie* obvious.

The Examiner states that the "recitation 'differential diagnosis of ischemic and hemorrhagic cerebral events' has not been give patentable weight because the recitation occurs in the preamble."

Applicants notes that independent Claim 24 has been amended to include a step in which a determination is made as to whether the patient condition is an ischemic or hemorrhagic cerebral event.

Reconsideration and withdrawal of this rejection under 35 U.S. C. § 103(a) are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 341-0036.

Respectfully submitted,

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Dated: March 12, 2002

MARKED UP VERSION OF AMENDMENTS

Claim Amendments Under 37 C.F.R. § 1.121(c)(1)(ii)

21. (Twice Amended) A method for the differential diagnosis of ischemic and hemorrhagic cerebral events comprising:

a. analyzing a body fluid of a patient to detect presence and concentration level of one or more ischemic marker proteins selected from the group consisting of myelin basic protein (MBP), the beta isoform of S100 protein (S100), and neuronal specific enolase (NSE) [and combinations thereof], said analyzing comprising contacting said one or more ischemic marker proteins with a reagent capable of detecting said marker proteins, and removing reagent that does not detect said marker proteins,

b. analyzing a body fluid of said patient to detect presence and concentration level of a brain endothelial cell membrane protein, said analyzing comprising contacting said brain endothelial cell membrane protein with a reagent capable of detecting said endothelial cell membrane protein, and removing reagent that does not detect said brain endothelial cell membrane protein, [and]

c. comparing the concentration level of each protein [any proteins] detected in steps (a) and (b) to specific threshold values to determine [verify] the presence of statistically significant concentrations thereof [of at least about two standard deviations above normal levels ; and],

d. assessing patient condition by comparing said presence or absence of statistically significant concentrations of said [proteins] protein in accordance with an analytical flow chart; and

[whereby differential diagnosis of an ischemic or hemorrhagic cerebral event is enabled.]

e. determining whether the patient condition assessed in step d is an ischemic cerebral event or an hemorrhagic cerebral event.

23. (Twice Amended) A method as defined in claim 21 wherein said body fluid is selected from the group consisting of blood, a blood [components] product and cerebrospinal fluid.

24. (Twice Amended) A method as defined in claim 21 wherein said brain endothelial cell membrane protein is selected from one or more of the group consisting of Thrombomodulin, Glucose Transporter I in the dimeric or tetrameric form, Neurothelin, Gamma Glutamyl Transpeptidase, and P-glycoprotein [and combinations thereof].

26. (Twice Amended) A method as defined in claim 21 further comprising [including]: analyzing said body fluid to detect presence and concentration level of a secondary marker protein, said secondary marker protein being from the cell type of one of said [which is cell type specific with respect to one of said] myelin basic protein, beta isoform of S100 protein or neuronal specific enolase, whereby the time of onset of a hemorrhagic or ischemic cerebral event can be determined.

34. (Amended) The method in accordance with claim 21 wherein in [said] step e, if MBP, S100, NSE and brain endothelial cell membrane proteins are assessed in step a and b, and only said NSE is elevated, than said patient condition is an ischemic cerebral event; or wherein in step e if MBP, S100, NSE and brain endothelial cell membrane protein are assessed in step a and b, and only said brain endothelial cell membrane protein is elevated, than said patient condition is an ischemic cerebral event; or wherein in step e, if S100 is present then said patient condition is an ischemic cerebral event; or wherein in step e, if NSE along with any of MBP, S100 or a brain endothelial cell membrane protein are present, then said patient condition is an ischemic cerebral event, or wherein in step e, if brain endothelial cell membrane protein, with any of MBP, NSE, or S100 are present, then said patient condition is an ischemic cerebral event; or wherein in step e, if S100 is present with elevated NSE and normal levels of brain endothelial cell membrane protein, then said patient condition is an ischemic cerebral event; or wherein in step e, if S100 is present alone, or along with elevated NSE or Thrombomodulin (Tm), then said patient condition is an ischemic cerebral event; or wherein in step e, if MBP is present at a level 200 times normal or greater, then said patient condition is a hemorrhagic cerebral event; or wherein in step e, if S100 and NSE levels are elevated, and MBP and Tm levels are normal, then said patient condition is a hemorrhagic cerebral event; or wherein in step e, if S100 and MBP are elevated, then said patient condition is a hemorrhagic cerebral event [of assessing patient condition includes:

1) initially concluding that a brain injury has occurred when one or more proteins are present;
2) further concluding that said brain injury is a TIA if only NSE is present;
3) further concluding that said brain injury is a lacunar infarct if only a brain endothelial cell membrane protein is present;
4) further concluding that said brain injury is an intracerebral hemorrhage if MBP is present at a level equal to or greater than about 200 times normal levels;
5) further concluding that said brain injury is a cerebral infarct if S100 is present; and
6) further concluding that said brain injury is a subarachnoid hemorrhage if S100 and NSE are present].

40. (Amended) A method for [the] determining that brain injury has occurred comprising:
(a) analyzing a body fluid of a patient to detect presence and concentration level of two or more proteins selected from the group consisting of myelin basic protein (MBP), the beta isoform of S100 protein (S100), neuronal specific enolase (NSE) and a brain endothelial cell membrane protein;
(b) comparing the concentration level of each protein [proteins] detected in step (a) to specific threshold values to determine [verify] the presence of a statistically significant concentration thereof; and
(c) determining if two or more of said proteins are [is] present in a [statically] statistically significant concentration, wherein the presence of two or more of said proteins in a statistically significant concentration is indicative that [is evidence that] an injury to the brain has occurred.

41. (Amended) A method for diagnosing an ischemic or hemorrhagic cerebral event comprising:
(a) analyzing a body fluid of a patient to detect the presence and concentration level of four proteins comprising myelin basic protein (MBP), the beta isoform of S100 protein (S100), neuronal specific enolase (NSE) and a brain endothelial cell membrane protein;

(b) comparing the concentration level of each said protein [proteins] detected in step (a) to specific threshold values to determine [verify] the presence of a statistically significant concentration thereof; [and]

(c) assessing patient condition by comparing said presence or absence of statistically significant concentrations of said proteins in accordance with an analytical flow chart; and

[wherein diagnosis of an ischemic or hemorrhagic cerebral event is enabled.]

(d) determining whether the patient condition assessed in step c is an ischemic cerebral event or an hemorrhagic cerebral event.

45. (Amended) The method of claim 44, wherein said first sample and said second sample [and said second samples] of body fluid are taken at different times.

46. (Amended) The method of claim 41 wherein step (c) comprises determining if said one or more of said proteins are present at a [statically] statistically significant concentration wherein the presence of one or more of said proteins is indicative [evidence] that injury to the brain has occurred.

47. (Amended) The method of claim 41 further comprising assessing [wherein step (c) comprises assessing] the type of brain injury wherein the presence of only NSE at a statistically significant concentration is indicative [evidence] that said brain injury is a transitory ischemic attack (TIA).

48. (Amended) The method of claim 41 further comprising [wherein step (c) comprises] assessing the type of brain injury wherein the presence of NSE and one or more proteins selected from the group consisting of MBP, S100, and a brain endothelial cell membrane protein at a statistically significant concentration is indicative [evidence] that said brain injury is a cerebral infarction.

49. (Amended) The method of [claims] claim 41 further comprising [wherein step (c) comprises] assessing the type of brain injury wherein the presence of only a brain

endothelial cell membrane protein at a statistically significant concentration is indicative [evidence] that said brain injury is a lunar infarction.

50. (Amended) The method of claim 41 further comprising [wherein step (c) comprises] assessing the type of brain injury wherein the presence of a brain endothelial cell membrane protein and one or more proteins selected from the group consisting of MBP, S100, and NSE at statistically significant concentrations is indicative [evidence] that said brain injury is a cerebral infarction.

51. (Amended) The method of claim 41 further comprising [wherein step (c) comprises] assessing the type of brain injury wherein the presence of MBP at a concentration of greater than about 200 times the normal level is indicative [evidence] that said brain injury is an intracerebral hemorrhage.

52. (Amended) The method of claim 41 further comprising [wherein step (c) comprises] assessing the type of brain injury wherein the presence of S100 at a statistically significant concentration is indicative [evidence] that said brain injury is a cerebral infarction or a subarachnoid hemorrhage.

53. (Amended) The method of claim 41 further comprising [wherein step (c) further comprises] assessing the type of brain injury wherein the presence of S100 and NSE at a statistically [statically] significant concentration [and the absence of any other markers] is indicative [evidence] that said brain injury is a subarachnoid hemorrhage.